METHODS AND COMPOSITIONS FOR TREATMENT OF ION IMBALANCES

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 10/814,527, filed on Mar. 30, 2004, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

At present, approximately 58 million American adults have hypertension, and its direct and indirect costs are estimated to be more than a quarter of a trillion dollars a year. Hypertension is considered to be the leading factor for stroke and is associated with a high rate of morbidity and mortality when diagnosed in the late stages. Hypertension is a disorder characterized by high blood pressure, i.e., systolic pressure consistently higher than about 140 or diastolic blood pressure consistently over about 90. Many factors affect blood pressure including volume of fluid in the body, salt content of the body, condition of the kidneys, nervous system, or blood vessels, and levels of various hormones in the body. 35% of Caucasian and 65% of African-American hypertension patients are characterized by salt/water retention. Hypertension and diabetes are the most common causes of End Stage Renal Disease (ESRD). The non-pharmacological approach to treating hypertension consists of salt restriction, weight control, and stress management. Control of sodium intake prevents one third of hypertension cases and is a useful adjunct therapy in another third of the cases.

The National Heart, Lung, and Blood Institute (NHLBI) recommends that as part of an overall healthy diet, Americans should consume no more than 2.4 gm (100 mmol) of sodium per day. This equals about 6 grams of sodium chloride. However, the average American diet consists of an estimated 8-12 gm of salt per day. In fact, the recommended salt intake is even lower for patients with late stage renal disease and those at risk of developing hypertension.

Common hypertension treatments include calcium channel blockers, diuretics, beta blockers, alpha blockers, anxiety medication, ACE inhibitors and vasodilators. Recent studies recommend that diuretics be used as the preferred initial stand-alone treatment or as part of a combination treatment for patients suffering from hypertension.

Diuretics are drugs that increase the rate of urine flow by interfering with the sodium and water re-absorption in the nephrons. In general, they increase the rate of sodium excretion from the body. Sodium is the main determinant of the water volume outside of the cells (referred to as extra cellular water). A diuretic that causes sodium to be excreted in the urine decreases the volume of the extra cellular water. The increase in sodium excretion restores salt homeostasis and lower tonicity which ultimately translates into lower blood pressure. As the body regulates intra and extra cellular sodium concentration within a very narrow window, the excretion of salt is usually accompanied by the loss of a proportional amount of water. Diuretics fall into four classes depending on their mode and locus of action:

a. carbonic anhydrase inhibitors such as acetazolamide inhibit the absorption of $NaHCO_3$ and NaCl in the proximal tubule;
b. loop diuretics such as furosemide, acting on the loop of Henle by inhibiting the Na^{+}™/K^{+}/$2Cl^{-}$ transporters;
c. thiazide type diuretics which inhibit Na^{+}/Cl^{-} cotransporters in the distal tubule;

d. potassium sparing diuretics acting on the collecting duct, they decrease the sodium absorption while sparing K^{+} (i.e., as opposed to the other three categories that promote loss of potassium).

Diuretics are not always effective therapies as they have undesired side effects. The imbalance in the anions induced by sodium transport modification tends to create complications such as acidosis or alkalosis. One of the limitations of diuretic therapy is "diuretic resistance". One definition of diuretic resistance is the failure to excrete at least 90 mmol of sodium within 72 hrs of a 160 mg oral furosemide dose given twice a day. This effect is caused by one or combination of mechanisms: (i) a change in the pharmacokinetic profile of loop diuretics, (ii) compensation of sodium absorption at distal nephron, and (iii) diminished nephron response. Loop diuretics, such as furosemide, exhibit a blood ceiling concentration where the fractional excretion of sodium is maximal. This ceiling effect has serious implications for patients who hardly respond to sub ceiling concentrations. These patients require continuous infusion of the drug to achieve the desired sodium excretion level. Despite several attempts to improve the drug profile or its bioavailability the results of these therapies remain less than would be desired.

Diuretic resistance is thought to happen in one out of three patients with congestive heart failure (CHF). As patients prescribed with a diuretic must adhere to a low sodium diet, another cause of failure of diuretic therapy is the inability of patients to comply with such a low salt diet.

Edema refers to the accumulation of abnormally large fluid volumes in the intercellular space of the body as a result of excessive sodium retention. Edema may be associated with renal insufficiency, nephritic syndrome, nephrotic syndrome, cardiac insufficiency, or hepatic failure. When the mechanisms regulating sodium balance in the body are disrupted, the accumulation of sodium leads to a compensatory accumulation of fluid (to rectify the osmotic imbalance) and observable edema. In patients with functioning kidneys, edema can be treated by limiting sodium intake and by the use of diuretics, which cause the body to excrete more water in the urine (Brater, D. C. (1992) "Clinical pharmacology of loop diuretics in health and disease." Eur Heart J 13 Suppl G: 10-4 and Brater, D. C. (1993) "Resistance to diuretics: mechanisms and clinical implications." Adv Nephrol Necker Hosp 22: 349-69). Diuretics are ineffective in patients who have reduced renal functions and also certain patient populations are non-responsive to diuretics (Brater, D. C. (1981) "Resistance to diuretics: emphasis on a pharmacological perspective." *Drugs* 22(6): 477-94 and Brater, D. C. (1985) "Resistance to loop diuretics. Why it happens and what to do about it." *Drugs* 30(5): 427-43).

Several studies have demonstrated that scavenging of instestinal sodium is possible. However, the amount of resin required for this purpose (in general from 60-100 g/day) is considered unacceptably high for modern therapy. The large doses reflect the low in vitro and lower in vivo binding capacity of these resins. Even in the presence of high sodium diets, sulfonic resins do not remove more than 1 mEq Na^{+}/gm, carboxylic resins not more than 2 mEq Na^{+}/gm and phosphonic resins not more than 0.8 mEq Na^{+}/g (Fourman, P. (1953) "Capacity of a cationic exchange resin (zeo-karb 225) in vivo." *Br Med J* 1(4809): 544-6; Heming, A. E. and T. L. Flanagan (1953) "Considerations in the selection of cation exchange resins for therapeutic use." *Ann NY Acad Sci* 57(3): 239-51; and McChesney, E. W., F. C. Nachod, et al. (1953) "Some aspects of cation exchange resins as therapeutic agents for sodium removal." *Ann NY Acad Sci* 57(3): 252-9). Typically, the resins retained only around 25% or less of their